SEARCH FOR PCT

24apr01 08:34:39 User208600 Session D1389.1
File 155:MEDLINE(R) 1966-2001/May W2 (c) format only 2000 Dialog Corporation

Set	Items	Description
S1	3	E6-E7
S2	4	CARD(W)4
S3	4739	CARD
S4	31872	DC="G4.335.139.160."
S5	3618	"CASPASES"
S6	26	S3 AND S4
S7	22	S3 AND S5
S8	17	S6 AND S7
S9	9	S6 NOT S8
S10	5	S7 NOT S8
S11	9726	"APOPTOSIS" NOT (S4 OR S5)
S12	7	S11 AND S3
S13	153	CASPASE? AND RECRUIT? NOT CARD
S14	121	S13 AND S4
S15	107	S13 AND S5
S16	91	S14 AND S15
S17	30	S14 NOT S16
S18	16	S15 NOT S16

Ref	Items	Index-term
E1	1	CARCYOLOGICAL
E2	1	CARCO
E3	4739	*CARD
E4	2	CARD PROTEIN
E5	950	CARD SYSTEMS //PUNCHED (PUNCHED-CARD SYSTEMS)
E6	2	CARD-CONTAINIG INTERLEUKIN (IL)-1 BETA CONVERT
E7	1	CARD-CONTAINING INTERLEUKIN (IL)-1 BETA CONVER
E8	1	CARD-COSALDON
E9	5	CARDA
E10	4	CARDAC
E11	2	CARDACA
E12	1	CARDACO

Ref	Items	RT	Index-term
E1	1		APOPTOSIN
E2	23		APOPTOSING
E3	41911	10	*APOPTOSIS
E4	10240		APOPTOSIS --DRUG EFFECTS --DE
E5	3038		APOPTOSIS --GENETICS --GE
E6	1931		APOPTOSIS --IMMUNOLOGY --IM
E7	6873		APOPTOSIS --PHYSIOLOGY --PH
E8	1064		APOPTOSIS --RADIATION EFFECTS --RE
E9	27		APOPTOSIS INDUCING FACTOR
E10	1		APOPTOSIS INHIBITOR API5L1
E11	1		APOPTOSIS PROTEIN INHIBITOR, PORCINE
E12	1		APOPTOSIS REGULATOR MTD

Ref	Items	Type	RT	Index-term
R1	41911		10	*APOPTOSIS
R2	31872	X		DC=G4.335.139.160. (APOPTOSIS)
R3	0	X	1	CELL DEATH, PROGRAMMED
R4	869	R	7	CASPASE 1
R5	3618	R	4	CASPASES
R6	404	R	5	CLONAL DELETION
R7	2148	R	6	IN SITU NICK-END LABELING
R8	2093	R	6	SUPERANTIGENS
R9	8258	B	6	CELL DEATH
R10	84	N	2	ANOIKIS
R11	3989	N	6	DNA FRAGMENTATION

1/6/1 10920386 21092790
Alteration of caspases and apoptosis-related proteins in brains of patients with Alzheimer's disease. Feb 16 2001

1/5/2 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
10012005 99370680
The modular nature of apoptotic signaling proteins.
Hofmann K
MEMOREC Stoffel GmbH, Koln, Germany. Kay.Hofmann@memorec.com
Cellular and molecular life sciences (SWITZERLAND) Jul 1999, 55 (8-9) p1113-28, ISSN 14[illegible]X Journal Code: CLE Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
JOURNAL ANNOUNCEMENT: 9911 Subfile: INDEX MEDICUS
Apoptosis, initiated by a variety of stimuli, is a physiological process that engages a well-ordered signaling cascade, eventually leading to the controlled death of the cell. The most extensively studied apoptotic stimulus is the binding of death receptors related to CD95 (Fas/Apo1) by their respective ligands. During the last years, a considerable number of proteins have been identified which act together in the receptor-proximal part of the signaling pathway. Based on localized regions of sequence similarity, it has been predicted that these proteins consist of several independently folding domains. In several cases these predictions have been confirmed by structural studies; in other cases they are at least supported by experimental data. This review focuses on the three most widespread domain families found in the apoptotic signaling proteins: the death domain, the death effector domain and the caspase recruitment domain. The recently discovered analogies between these domains, both in structure and in function, have shed some light on the overall architecture of the pathway leading from death receptor ligation to the activation of caspases and eventually to the apoptotic phenotype. (108 Refs.)
Tags: Human
Descriptors: *Apoptosis; *Protein Structure, Tertiary; *Signal Transduction; Amino Acid Sequence; Antigens, CD--Chemistry--CH; Antigens, CD--Physiology--PH; Antigens, CD95--Chemistry--CH; Antigens, CD95 --Physiology--PH; Carrier Proteins--Chemistry--CH; Carrier Proteins --Physiology--PH; Caspases--Metabolism--ME; Enzyme Activation; Fatty Acid Desaturases--Chemistry--CH; Fatty Acid Desaturases--Physiology--PH; Helminth Proteins--Chemistry--CH; Helminth Proteins--Physiology--PH; Infant, Newborn; Membrane Glycoproteins--Chemistry--CH; Membrane Glycoproteins--Physiology--PH; Molecular Sequence Data; Multigene Family; Protein-Serine-Threonine Kinases--Chemistry--CH; Protein-Serine-Threonine Kinases--Physiology--PH; Proteins--Chemistry--CH; Proteins--Physiology--PH ; Receptors, Tumor Necrosis Factor--Chemistry--CH; Receptors, Tumor Necrosis Factor--Physiology--PH; Sequence Alignment; Sequence Homology, Amino Acid; Structure-Activity Relationship
CAS Registry No.: 0 (receptor interacting protein); 0 (tumor necrosis factor receptor 55); 0 (Antigens, CD); 0 (Antigens, CD95); 0 (Carrier Proteins); 0 (FasL protein); 0 (Helminth Proteins); 0 (Membrane Glycoproteins); 0 (MORT1 protein); 0 (Proteins); 0 (Receptors, Tumor Necrosis Factor); 0 (RAIDD protein); 0 (TNF receptor-associated factor 1)
Enzyme No.: EC 1.14.99.- (Fad7 protein, Arabidopsis); EC 1.14.99.- (Fatty Acid Desaturases); EC 2.7.10 (Protein-Serine-Threonine Kinases); EC 2.7.10.- (CARD-containig interleukin (IL)-1 beta converting enzyme); EC 3.4.22.- (Caspases)

1/5/3 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
09669186 98381580
Identification of CARDIAK, a RIP-like kinase that associates with caspase-1.
Thome M; Hofmann K; Burns K; Martinon F; Bodmer JL; Mattmann C; Tschopp J
Institute of Biochemistry, University of Lausanne, Epalinges, Switzerland.
Current biology (ENGLAND) Jul 16 1998, 8 (15) p885-8, ISSN 0960-9822
Journal Code: B44 Languages: ENGLISH Document type: JOURNAL ARTICLE
JOURNAL ANNOUNCEMENT: 9901 Subfile: INDEX MEDICUS
Members of the tumor necrosis factor receptor (TNFR) superfamily have an important role in the induction of cellular signals resulting in cell growth, differentiation and death. TNFR-1 recruits and assembles a signaling complex containing a number of death domain (DD)-containing proteins, including the adaptor protein TRADD and the serine/threonine kinase RIP, which mediates TNF-induced NF-kappa B activation. RIP also recruits caspase-2 to the TNFR-1 signaling complex via the adaptor protein RAIDD, which contains a DD and a caspase-recruiting domain (CARD). Here, we have identified a RIP-like kinase, termed CARDIAK (for CARD-containing interleukin (IL)-1 beta converting enzyme (ICE) associated kinase), which contains a serine/threonine kinase domain and a carboxy-terminal CARD. Overexpression of CARDIAK induced the activation of both NF-kappa B and Jun N-terminal kinase (JNK). CARDIAK interacted with the TNFR-associated factors TRAF-1 and TRAF-2, and a dominant-negative form of TRAF-2 inhibited CARDIAK-induced NF-kappa B activation. Interestingly, CARDIAK specifically interacted with the CARD of caspase-1 (previously known as ICE), and this interaction correlated with the processing of pro-caspase-1 and the formation of the active p20 subunit of caspase-1. Together, these data suggest that CARDIAK may be involved in NF-kappa B/JNK signaling and in the generation of the proinflammatory cytokine IL-1 beta through activation of caspase-1.
Tags: Human; Support, Non-U.S. Gov't
Descriptors: *Caspase 1--Metabolism--ME; *Protein-Serine-Threonine Kinases--Metabolism--ME; Amino Acid Sequence; Base Sequence; Ca(2+)-Calmodulin Dependent Protein Kinase--Metabolism--ME; Cell Line, Transformed; Molecular Sequence Data; NF-kappa B--Metabolism--ME;

Protein-Serine-Threonine Kinases--Genetics[illegible]Proteins--Chemistry--CH; Proteins--Metabolism--ME; Receptors, Tumor N[illegible]osis Factor--Metabolism--ME ; Sequence Homology, Amino Acid
Molecular Sequence Databank No.: GENBANK/AF064824
CAS Registry No.: 0 (receptor interacting protein); 0 (NF-kappa B); 0 (Proteins); 0 (Receptors, Tumor Necrosis Factor); 0 (TNF receptor-associated factor 1); 0 (TNF receptor-associated factor 2) Enzyme No.: EC 2.7.10 (Protein-Serine-Threonine Kinases); EC 2.7.10.- (c-Jun amino-terminal kinase); EC 2.7.10.- (Ca(2+)-Calmodulin Dependent Protein Kinase); EC 2.7.10.- (CARD-containig interleukin (IL)-1 beta converting enzyme); EC 3.4.22.36 (Caspase 1)

2/6/1 07723626 94140985
Parallel comparison of accuracy of API 20E, Vitek GNI, MicroScan Walk/Away Rapid ID, and Becton Dickinson Cobas Micro ID-E/NF for identification of members of the family Enterobacteriaceae and common gram-negative, non-glucose-fermenting bacilli. Dec 1993

2/6/2 07496186 93160019
Combination or mild single agent chemotherapy for advanced breast cancer? CMF vs epirubicin measuring quality of life. Feb 1993

2/6/3 07190880 93105662
The efficacy and tolerability of controlled-release dihydrocodeine tablets and combination dextropropoxyphene/paracetamol tablets in patients with severe osteoarthritis of the hips. 1992

2/6/4 03594767 83048755
Tiaramide--a new oral drug for the treatment of asthma. Oct 1982

8/7/1 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
10920386 21092790
Alteration of caspases and apoptosis-related proteins in brains of patients with Alzheimer's disease.
Engidawork E; Gulesserian T; Yoo BC; Cairns N; Lubec G
Department of Pediatrics, University of Vienna, Vienna, Austria.
Biochemical and biophysical research communications (United States) Feb 16 2001, 281 (1) p84-93, ISSN 0006-291X Journal Code: 9Y8 Languages: ENGLISH Document type: Journal Article
Dysregulated programmed cell death or apoptosis is suggested to be involved in the pathogenesis of Alzheimer's disease (AD). Caspases , the major effectors of apoptosis, are cysteine proteases that cleave crucial substrate proteins exclusively after aspartate residues. The activity of caspases are delicately regulated by a variety of proteins that possess distinct domains for protein-protein interaction. To further substantiate the role of apoptosis in AD, we investigated the levels of nine different proteins involved in apoptosis by Western blot technique in frontal cortex and cerebellum of control and AD subjects. The protein levels of caspase-3, -8, and -9, DFF45 (DNA fragmentation factor 45), and FLIP (Fas associated death domain (FADD)-like interleukin-1beta-converting enzyme inhibitory proteins) were decreased, whereas those of ARC (apoptosis repressor with caspase recruitment domain) and RICK (Receptor interacting protein (RIP)-like interacting CLARP kinase) increased in AD. In contrast, cytochrome c and Apaf-1 (apoptosis protease activating factor-1) were unchanged. Regression analysis revealed no correlation between levels of protein and postmortem interval. However, inconsistent correlation was found between age and levels of proteins as well as among the levels of individual proteins. The current findings showed that dysregulation of apoptotic proteins indeed exists in AD brain and support the notion that it may contribute to neuropathology of AD. The study further hints that apoptosis in AD may occur via the death receptor pathway independent of cytochrome c. Hence, therapeutic strategies that ablate caspase activation may be of some benefit for AD sufferers.

8/7/2 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
10695820 20576268
CARD9 is a novel caspase recruitment domain-containing protein that interacts with BCL10/CLAP and activates NF-kappa B.
Bertin J; Guo Y; Wang L; Srinivasula SM; Jacobson MD; Poyet JL; Merriam S ; Du MQ; Dyer MJ; Robison KE; DiStefano PS; Alnemri ES
Millennium Pharmaceuticals, Inc., Cambridge, Massachusetts 02139, USA. bertin@mpi.com
Journal of biological chemistry (UNITED STATES) Dec 29 2000, 275 (52) p41082-6, ISSN 0021-9258 Journal Code: HIV Contract/Grant No.: CA85421, CA, NCI Languages: ENGLISH Document type: Journal Article
BCL10/CLAP is an activator of apoptosis and NF-kappaB signaling pathways and has been implicated in B cell lymphomas of mucosa-associated lymphoid tissue. Although its role in apoptosis remains to be determined, BCL10 likely activates NF-kappaB through the IKK complex in response to upstream stimuli. The N-terminal caspase recruitment domain (CARD) of BCL10 has been proposed to function as an activation domain that mediates homophilic interactions with an upstream CARD -containing NF-kappaB activator. To identify upstream signaling partners of BCL10, we performed a mammalian two-hybrid analysis and identified CARD9 as a novel CARD -containing protein that interacts selectively with the C[illegible]ctivation domain of BCL10. When expressed in cells, CARD9 binds t[illegible]CL10 and activates NF-kappaB. Furthermore, endogenous CARD9 is found associated with BCL10 suggesting that both proteins form a pre-existing signaling complex within cells. CARD9 also self-associates and contains extensive coiled-coil motifs that may function as oligomerization domains. We propose here that CARD9 is an upstream activator of BCL10 and NF-kappaB signaling.

8/7/3 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
10647463 20552140
Activation of a caspase-9-mediated apoptotic pathway by subcellular redistribution of the novel caspase recruitment domain protein TMS1.
McConnell BB; Vertino PM
Department of Radiation Oncology and the Winship Cancer Institute, Emory University School of Medicine, Atlanta, Georgia 30322, USA.
Cancer research (UNITED STATES) Nov 15 2000, 60 (22) p6243-7, ISSN 0008-5472 Journal Code: CNF Contract/Grant No.: 1 F32 CA83289-01, CA, NCI; CA77337, CA, NCI Languages: ENGLISH Document type: Journal Article
Genetic and epigenetic alterations affecting proteins involved in apoptosis can contribute to the establishment and progression of cancer. Recently, our laboratory has isolated a novel gene, TMS1, that is aberrantly methylated and silenced in a significant proportion of human breast cancers. TMS1 contains a caspase recruitment domain (CARD), suggesting a role in caspase-mediated cell death. In the present study, we characterize the participation of TMS1 in apoptosis and examine the subcellular localization of the protein. Inducible expression of TMS1 inhibited cellular proliferation and induced DNA fragmentation in a time-dependent manner. These apoptotic events were blocked by the general caspase inhibitor, Z-VAD-fmk. The ability of TMS1 to trigger apoptosis was also suppressed by a dominant negative form of caspase-9 but not by a dominant negative form of caspase-8, indicating that TMS1 functions through activation of caspase-9. Unlike a number of other CARD -containing proteins, TMS1 did not activate nuclear factor kappaB-dependent transcription, consistent with a proapoptotic role for TMS1 in death signaling pathways. Timed localization studies revealed that TMS1-induced apoptosis was accompanied by the redistribution of TMS1 from the cytoplasm to perinuclear spherical structures. Whereas the apoptotic activity of TMS1 was blocked by caspase inhibition, the formation of TMS1-containing subcellular structures was not, suggesting that the redistribution of TMS1 precedes caspase activation. Both the proapoptotic activity of TMS1 and aggregate formation were dependent on the CARD . In summary, the data indicate that TMS1-induced apoptosis proceeds through a CARD -dependent aggregation step followed by activation of a caspase-9-mediated pathway.

8/7/4 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
10647462 20552139
TMS1, a novel proapoptotic caspase recruitment domain protein, is a target of methylation-induced gene silencing in human breast cancers.
Conway KE; McConnell BB; Bowring CE; Donald CD; Warren ST; Vertino PM
Department of Radiation Oncology and the Winship Cancer Institute, Emory University School of Medicine, Atlanta, Georgia 30322, USA.
Cancer research (UNITED STATES) Nov 15 2000, 60 (22) p6236-42, ISSN 0008-5472 Journal Code: CNF
Contract/Grant No.: 1RO1-CA77337, CA, NCI; F32-CA83289, CA, NCI Languages: ENGLISH Document type: Journal Article
Gene silencing associated with aberrant methylation of promoter region CpG islands is an acquired epigenetic alteration that serves as an alternative to genetic defects in the inactivation of tumor suppressor and other genes in human cancers. The hypothesis that aberrant methylation plays a direct causal role in carcinogenesis hinges on the question of whether aberrant methylation is sufficient to drive gene silencing. To identify downstream targets of methylation-induced gene silencing, we used a human cell model in which aberrant CpG island methylation is induced by ectopic expression of DNA methyltransferase. Here we report the isolation and characterization of TMS1 (target of methylation-induced silencing), a novel CpG island-associated gene that becomes hypermethylated and silenced in cells overexpressing DNA cytosine-5-methyltransferase-1. We also show that TMS1 is aberrantly methylated and silenced in human breast cancer cells. Forty percent (11 of 27) of primary breast tumors exhibited aberrant methylation of TMS1. TMS1 is localized to chromosome 16p11.2-12.1 and encodes a 22-kDa predicted protein containing a COOH-terminal caspase recruitment domain, a recently described protein interaction motif found in apoptotic signaling molecules. Ectopic expression of TMS1 induced apoptosis in 293 cells and inhibited the survival of human breast cancer cells. The data suggest that methylation-mediated silencing of TMS1 confers a survival advantage by allowing cells to escape from apoptosis, supporting a new role for aberrant methylation in breast tumorigenesis.

8/7/5 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
10623036 20527933

Mechanisms of apoptosis.
Reed JC
Burnham Institute, La Jolla, California 92037, USA. jreed@burnham-inst.org
American journal of pathology (UNITED STATES) Nov 2000, 157 (5) p1415-30, ISSN 0002-9440 Journal Code: 3RS
Languages: ENGLISH Document type: Lectures
Programmed cell deat diseases.

8/7/6 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
10566732 20394289
Negative regulation of the Apaf-1 apoptosome by Hsp70.
Saleh A; Srinivasula SM; Balkir L; Robbins PD; Alnemri ES
Center for Apoptosis Research and Department of Microbiology and Immunology, Kimmel Cancer Institute, Thomas Jefferson University, Philadelphia, Pennsylvania 19107, USA.
Nature cell biology (ENGLAND) Aug 2000, 2 (8) p476-83, ISSN 1465-7392 Journal Code: DIQ
Contract/Grant No.: AG13487, AG, NIA; AG14357, AG, NIA; CA55227, CA, NCI Languages: ENGLISH Document type: JOURNAL ARTICLE
Release of cytochrome c from mitochondria by apoptotic signals induces ATP/dATP-dependent formation of the oligomeric Apaf-1-caspase-9 apoptosome. Here we show that the documented anti-apoptotic effect of the principal heat-shock protein, Hsp70, is mediated through its direct association with the caspase-recruitment domain (CARD) of Apaf-1 and through inhibition of apoptosome formation. The interaction between Hsp70 and Apaf-1 prevents oligomerization of Apaf-1 and association of Apaf-1 with procaspase-9. On the basis of these results, we propose that resistance to apoptosis exhibited by stressed cells and some tumours, which constitutively express high levels of Hsp70, may be due in part to modulation of Apaf-1 function by Hsp70.

8/7/7 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
10385609 20180358
Subcellular localization and CARD -dependent oligomerization of the death adaptor RAIDD.
Shearwin-Whyatt LM; Harvey NL; Kumar S
Hanson Centre for Cancer Research, Institute of Medical and Veterinary Science, Frome Road, Adelaide, Australia.
Cell death and differentiation (ENGLAND) Feb 2000, 7 (2) p155-65, ISSN 1350-9047 Journal Code: C7U Languages: ENGLISH
Document type: JOURNAL ARTICLE
RAIDD, a caspase recruitment domain (CARD) containing molecule, interacts with procaspase-2 in a CARD -dependent manner. This interaction has been suggested to mediate the recruitment of caspase-2 to the tumour necrosis factor receptor 1 (TNFR1). In this paper we have studied the subcellular localization of RAIDD and its interaction with caspase-2. We demonstrate that endogenous RAIDD is mostly localized in the cytoplasm and to some extent in the nucleus. RAIDD localization is not affected by TNF-treatment of HeLa cells, but in cells ectopically expressing caspase-2, a fraction of RAIDD is recruited to the nucleus. In transfected cells, coexpression of RAIDD and caspase-2 leads to CARD -dependent colocalization of the two proteins to discrete subcellular structures. We further show that overexpression of the RAIDD-CARD results in the formation of filamentous structures due to CARD -mediated oligomerization. These structures were similar to death effector filaments (DEFs) formed by FADD and FLICE death effector domains (DEDs), and partially colocalized with DEFs. Our results suggest that similar to the DED, the RAIDD-CARD has the ability to form higher order complexes, believed to be important in apoptotic execution. We also present evidence that RAIDD-CARD oligomerization may be regulated by intramolecular folding of the RAIDD molecule.

8/7/8 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
10218776 20036508
ASC, a novel 22-kDa protein, aggregates during apoptosis of human promyelocytic leukemia HL-60 cells.
Masumoto J; Taniguchi S; Ayukawa K; Sarvotham H; Kishino T; Niika a N; Hidaka E; Katsuyama T; Higuchi T; Sagara J
Department of Molecular Oncology, Research Center on Aging and Adaptation, Shinshu University School of Medicine, Asahi 3-1-1, Matsumoto 390-8621, Nagano, Japan.
Journal of biological chemistry (UNITED STATES) Nov 26 1999, 274 (48) p33835-8, ISSN 0021-9258 Journal Code: HIV Languages: ENGLISH
Document type: JOURNAL ARTICLE
The cytoskeletal and/or nuclear matrix molecules responsible for morphological changes associated with apoptosis were identified using monoclonal antibodies (mAbs). We developed mAbs against Triton X-100-insoluble components of HL-60 cells pretreated with all-trans retinoic acid. In particular, one mAb recognized a 22-kDa protein that exhibited intriguing behavior by forming an aggregate and appearing as a speck during apoptosis induced b[illegible]oic acid and other anti-tumor drugs. Cloning and sequencing of its cD[illegible] revealed that this protein comprises 195 amino acids and that its C-terminal half has a caspase recruitment domain (CARD) motif, characteristic of numerous proteins involved in apoptotic signaling. We referred to this protein as ASC (apoptosis-associated speck-like protein containing a CARD). The ASC gene was mapped on chromosome 16p11.2-12. The antisense oligonucleotides of ASC were found to reduce the expression of ASC, and consequently, etoposide-mediated apoptosis of HL-60 cells was suppressed. Our results indicate that ASC is a novel member of the CARD -containing adaptor protein family.

8/7/9 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
10190779 99457304
Requirement of cooperative functions of two repeated death effector domains in caspase-8 and in MC159 for induction and inhibition of apoptosis, respectively.
Tsukumo SI; Yonehara S
Institute for Virus Research, Kyoto University, Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan.
Genes to cells (ENGLAND) Sep 1999, 4 (9) p541-9, ISSN 1356-9597 Journal Code: CUF Languages: ENGLISH Document type: JOURNAL ARTICLE
BACKGROUND: The death effector domain (DED), which functions as a domain for a homophilic protein interaction, plays a role in death receptor-mediated apoptosis. Two tandemly repeated DEDs in the prodomain of caspase-8 (Casp8NC-DED) and those in MC159 (viral FLIP) have been shown to positively and negatively regulate apoptosis, respectively, by binding to caspase-8 and/or Fas-associated death domain (FADD). However, characteristics of each DED in Casp8NC-DED and those in MC159 have not been well examined. RESULTS: We analysed deletion and chimera mutants of DEDs derived from Casp8NC-DED and MC159, and found that MC159 and Casp8NC-DED require the combined effects of the two repeated DEDs to exert their binding and biological activities. The carboxy-terminal DED of Casp8NC-DED (Casp8C-DED) has the potential to induce apoptosis, and the amino-terminal DED of MC159 showed a dominant inhibitory effect on apoptosis when combined with Casp8C-DED. In addition, the two repeated DEDs in Casp8NC-DED and MC159 were shown to regulate the activities of caspase differently from the caspase recruitment domain (CARD) in the prodomains of caspase-2, -9 and Apaf-1. CONCLUSIONS: Although each of the DEDs in Casp8NC-DED and MC159 has the potential to stimulate or inhibit apoptosis, the combination of the two-repeated DEDs is necessary for the DED-containing proteins to stimulate or inhibit apoptosis.

8/7/10 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
10166796 20013059
Crystal structure of Apaf-1 caspase recruitment domain: an alpha-helical Greek key fold for apoptotic signaling.
Vaughn DE; Rodriguez J; Lazebnik Y; Joshua-Tor L
W. M. Keck Structural Biology, Cold Spring Harbor, NY 11724, USA.
Journal of molecular biology (ENGLAND) Oct 29 1999, 293 (3) p439-47, ISSN 0022-2836 Journal Code: J6V Contract/Grant No.: CA 13106-25, CA, NCI
Languages: ENGLISH Document type: JOURNAL ARTICLE
The caspase recruitme Copyright 1999 Academic Press.

8/7/11 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
10128355 99214545
CIPER, a novel NF kappaB-activating protein containing a caspase recruitment domain with homology to Herpesvirus-2 protein E10.
Koseki T; Inohara N; Chen S; Carrio R; Merino J; Hottiger MO; Nabel GJ; Nunez G
Department of Pathology and Comprehensive Cancer Center, The University of Michigan Medical School, Ann Arbor, Michigan 48109, USA.
Journal of biological chemistry (UNITED STATES) Apr 9 1999, 274 (15) p9955-61, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: CA-64556, CA, NCI; CA-64421, CA, NCI Languages: ENGLISH Document type: JOURNAL ARTICLE
We have identified and characterized CIPER, a novel protein containing a caspase recruitment domain (CARD) in its N terminus and a C-terminal region rich in serine and threonine residues. The CARD of CIPER showed striking similarity to E10, a product of the equine herpesvirus-2. CIPER formed homodimers via its CARD and interacted with viral E10 but not with several apoptosis regulators containing CARDs including ARC, RAIDD, RICK, caspase-2, caspase-9, or Apaf-1. Expression of CIPER induced NF-kappaB activation, which was inhibited by dominant-negative NIK and a nonphosphorylable IkappaB-alpha mutant but not by dominant-negative RIP. Mutational analysis revealed that the N-terminal region of CIPER containing the CARD was sufficient and necessary for NF-kappaB-inducing activity. Point mutations in highly conserved residues in the CARD of CIPER disrupted the ability of CIPER to activate NF-kappaB and to form homodimers, indicating

that the CARD is essential for NF-kappaB activation and dimerization. We propose that CIPER acts in a NIK-dependent pathway of NF-kappaB activation.

8/7/12 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
10102107 98226784
ARC, an inhibitor of apoptosis expressed in skeletal muscle and heart that interacts selectively with caspases.
Koseki T; Inohara N; Chen S; Nunez G
Departments of Pathology and Comprehensive Cancer Center, University of Michigan Medical School, Ann Arbor, MI 48109, USA.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Apr 28 1998, 95 (9) p5156-60, ISSN 0027-8424 Journal Code: PV3
Contract/Grant No.: R01 CA64556-01, CA, NCI; K04 CA64421-01, CA, NCI
Languages: ENGLISH Document type: JOURNAL ARTICLE
We have identified and characterized ARC, apoptosis repressor with caspase recruitment domain (CARD). Sequence analysis revealed that ARC contains an N-terminal CARD fused to a C-terminal region rich in proline/glutamic acid residues. The CARD domain of ARC exhibited significant homology to the prodomains of apical caspases and the CARDs present in the cell death regulators Apaf-1 and RAIDD. Immunoprecipitation analysis revealed that ARC interacts with caspase-2, -8, and Caenorhabditis elegans CED-3, but not with caspase-1, -3, or -9. ARC inhibited apoptosis induced by caspase-8 and CED-3 but not that mediated by caspase-9. Further analysis showed that the enzymatic activity of caspase-8 was inhibited by ARC in 293T cells. Consistent with the inhibition of caspase-8, ARC attenuated apoptosis induced by FADD and TRADD and that triggered by stimulation of death receptors coupled to caspase-8, including CD95/Fas, tumor necrosis factor-R1, and TRAMP/DR3. Remarkably, the expression of human ARC was primarily restricted to skeletal muscle and cardiac tissue. Thus, ARC represents an inhibitor of apoptosis expressed in muscle that appears to selectively target caspases . Delivery of ARC by gene transfer or enhancement of its endogenous activity may provide a strategy for the treatment of diseases that are characterized by inappropriately increased cell death in muscle tissue.

8/7/13 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
10012005 99370680
The modular nature of apoptotic signaling proteins.
Hofmann K
MEMOREC Stoffel GmbH, Koln, Germany. Kay.Hofmann@memorec.com
Cellular and molecular life sciences (SWITZERLAND) Jul 1999, 55 (8-9) p1113-28, ISSN 1420-682X Journal Code: CLE Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Apoptosis, initiated by a variety of stimuli, is a physiological process that engages a well-ordered signaling cascade, eventually leading to the controlled death of the cell. The most extensively studied apoptotic stimulus is the binding of death receptors related to CD95 (Fas/Apo1) by their respective ligands. During the last years, a considerable number of proteins have been identified which act together in the receptor-proximal part of the signaling pathway. Based on localized regions of sequence similarity, it has been predicted that these proteins consist of several independently folding domains. In several cases these predictions have been confirmed by structural studies; in other cases they are at least supported by experimental data. This review focuses on the three most widespread domain families found in the apoptotic signaling proteins: the death domain, the death effector domain and the caspase recruitment domain. The recently discovered analogies between these domains, both in structure and in function, have shed some light on the overall architecture of the pathway leading from death receptor ligation to the activation of caspases and eventually to the apoptotic phenotype. (108 Refs.)

8/7/14 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
10005694 99321747
Role of cytochrome c and dATP/ATP hydrolysis in Apaf-1-mediated caspase-9 activation and apoptosis.
Hu Y; Benedict MA; Ding L; Nunez G
Department of Pathology and Comprehensive Cancer Center, University of Michigan Medical School, 1500 East Medical Center Drive, 4219 CCGC, Ann Arbor, MI 48109, USA.
EMBO journal (ENGLAND) Jul 1 1999, 18 (13) p3586-95, ISSN 0261-4189
Journal Code: EMB Contract/Grant No.: CA-64556, CA, NCI; 2T32HL07517, HL, NHLBI; CA-64421, CA, NCI Languages: ENGLISH Document type: JOURNAL ARTICLE
Apaf-1 plays a critical role in apoptosis by binding to and activating procaspase-9. We have identified a novel Apaf-1 cDNA encoding a protein of 1248 amino acids containing an insertion of 11 residues between the CARD and ATPase domains, and another 43 amino acid insertion creating an additional WD-40 repeat. The product of this Apaf-1 cDNA activated procaspase-9 in a cytochrome c and dATP/ATP-dependent manner. We used this Apaf-1 to show that Apaf-1 requires dATP/ATP hydrolysis to interact with cytochrome c, self-associate and bind to procaspase-9. A P-loop mutant (Apaf-1K160R) was unable to associate with Apaf-1 or bind to procaspase-9. Mutation of Met368 to Leu enabled Apaf-1 to self-associate and bind procaspase-9 independent of cytochrome c, though still requiring dATP/ATP for these activities. The Apaf-1M368L mutant exhibited greater ability to induce apoptosis compared with the wild-type Apaf-1. We also show that procaspase-9 can recruit procaspase-3 to the Apaf-1-procaspase-9 complex. Apaf-1(1-570), a mutant lacking the WD-40 repeats, associated with and activated procaspase-9, but failed to recruit procaspase-3 and induce apoptosis. These results suggest that the WD-40 repeats may be involved in procaspase-9-mediated procaspase-3 recruitment. These studies elucidate biochemical steps required for Apaf-1 to activate procaspase-9 and induce apoptosis.

8/7/15 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
09953770 99262599
Nod1, an Apaf-1-like activator of caspase-9 and nuclear factor-kappaB.
Inohara N; Koseki T; del Peso L; Hu Y; Yee C; Chen S; Carrio R; Merino J; Liu D; Ni J; Nunez G
Department of Pathology and Comprehensive Cancer Center, The University of Michigan Medical School, Ann Arbor, Michigan 48109, USA.
Journal of biological chemistry (UNITED STATES) May 21 1999, 274 (21) p14560-7, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: RO1 CA64556, CA, NCI; K04 CA64421, CA, NCI
Languages: ENGLISH Document type: JOURNAL ARTICLE
Ced-4 and Apaf-1 belong to a major class of apoptosis regulators that contain caspase-recruitment (CARD) and nucleotide-binding oligomerization domains. Nod1, a protein with an NH2-terminal CARD -linked to a nucleotide-binding domain and a COOH-terminal segment with multiple leucine-rich repeats, was identified. Nod-1 was found to bind to multiple caspases with long prodomains, but specifically activated caspase-9 and promoted caspase-9-induced apoptosis. As reported for Apaf-1, Nod1 required both the CARD and P-loop for function. Unlike Apaf-1, Nod1 induced activation of nuclear factor-kappa-B (NF-kappaB) and bound RICK, a CARD -containing kinase that also induces NF-kappaB activation. Nod1 mutants inhibited NF-kappaB activity induced by RICK, but not that resulting from tumor necrosis factor-alpha stimulation. Thus, Nod1 is a leucine-rich repeat-containing Apaf-1-like molecule that can regulate both apoptosis and NF-kappaB activation pathways.

8/7/16 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
09873973 99214546
Equine herpesvirus-2 E10 gene product, but not its cellular homologue, activates NF-kappaB transcription factor and c-Jun N-terminal kinase.
Thome M; Martinon F; Hofmann K; Rubio V; Steiner V; Schneider P; Mattmann C; Tschopp J
Institute of Biochemistry, University of Lausanne, Switzerland.
Journal of biological chemistry (UNITED STATES) Apr 9 1999, 274 (15) p9962-8, ISSN 0021-9258 Journal Code: HIV Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have previously reported on the death effector domain containing E8 gene product from equine herpesvirus-2, designated FLICE inhibitory protein (v-FLIP), and on its cellular homologue, c-FLIP, which inhibit the activation of caspase-8 by death receptors. Here we report on the structure and function of the E10 gene product of equine herpesvirus-2, designated v-CARMEN, and on its cellular homologue, c-CARMEN, which contain a caspase-recruiting domain (CARD) motif. c-CARMEN is highly homologous to the viral protein in its N-terminal CARD motif but differs in its C-terminal extension. v-CARMEN and c-CARMEN interact directly in a CARD -dependent manner yet reveal different binding specificities toward members of the tumor necrosis factor receptor-associated factor (TRAF) family. v-CARMEN binds to TRAF6 and weakly to TRAF3 and, upon overexpression, potently induces the c-Jun N-terminal kinase (JNK), p38, and nuclear factor (NF)-kappaB transcriptional pathways. c-CARMEN or truncated versions thereof do not appear to induce JNK and NF-kappaB activation by themselves, nor do they affect the JNK and NF-kappaB activating potential of v-CARMEN. Thus, in contrast to the cellular homologue, v-CARMEN may have additional properties in its unique C terminus that allow for an autonomous activator effect on NF-kappaB and JNK. Through activation of NF-kappaB, v-CARMEN may regulate the expression of the cellular and viral genes important for viral
replication.

8/7/17 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
09873928 99214590
mE10, a novel caspase recruitment domain-containing proapoptotic molecule.
Yan M; Lee J; Schilbach S; Goddard A; Dixit V
Department of Molecular Oncology, Genentech, Inc., South San Francisco, California 94080, USA.
Journal of biological chemistry (UNITED STATES) Apr 9 1999, 274 (15) p10287-92, ISSN 0021-9258 Journal Code: HIV Languages: ENGLISH

Document type: JOURNAL ARTICLE

Apoptotic signaling is mediated by homophilic interactions between conserved domains present in components of the death pathway. The death domain, death effector domain, and caspase recruitment domain (CARD) are examples of such interaction motifs. We have identified a novel mammalian CARD -containing adaptor molecule termed mE10 (mammalian E10). The N-terminal CARD of mE10 exhibits significant homology (47% identity and 64% similarity) to the CARD of a gene from Equine Herpesvirus type 2. The C-terminal region is unique. Overexpression of mE10 in MCF-7 human breast carcinoma cells induces apoptosis. Mutational analysis indicates that CARD -mediated mE10 oligomerization is essential for killing activity. The C terminus of mE10 bound to the zymogen form of caspase-9 and promoted its processing to the active dimeric species. Taken together, these data suggest a model where autoproteolytic activation of pro-caspase-9 is mediated by mE10-induced oligomerization.

9/7/1 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.

10843450 21097719

Bcl10 is a positive regulator of antigen receptor-induced activation of NF-kappaB and neural tube closure.

Ruland J; Duncan GS; Elia A; del Barco Barrantes I; Nguyen L; Plyte S; Millar DG; Bouchard D; Wakeham A; Ohashi PS; Mak TW

Amgen Institute, 620 University Avenue, Toronto, Ontario, Canada M5G 2 C1.

Cell (United States) Jan 12 2001, 104 (1) p33-42, ISSN 0092-8674

Journal Code: CQ4 Languages: ENGLISH Document type: Journal Article

Bcl10, a CARD -containing protein identified from the t(1;14)(p22;q32) breakpoint in MALT lymphomas, has been shown to induce apoptosis and activate NF-kappaB in vitro. We show that one-third of bcl10-/- embryos developed exencephaly, leading to embryonic lethality. Surprisingly, bcl10-/- cells retained susceptibility to various apoptotic stimuli in vivo and in vitro. However, surviving bcl10-/- mice were severely immunodeficient and bcl10-/- lymphocytes are defective in antigen receptor or PMA/Ionomycin-induced activation. Early tyrosine phosphorylation, MAPK and AP-I activation, and Ca2+ signaling were normal in mutant lymphocytes, but antigen receptor-induced NF-kappaB activation was absent. Thus, Bcl10 functions as a positive regulator of lymphocyte proliferation that specifically connects antigen receptor signaling in B and T cells to NF-kappaB activation.

9/7/2 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.

10568647 20428692

An induced proximity model for NF-kappa B activation in the Nod1/RICK and RIP signaling pathways.

Inohara N; Koseki T; Lin J; del Peso L; Lucas PC; Chen FF; Ogura Y; Nunez G

Department of Pathology and Comprehensive Cancer Center, The University of Michigan Medical School, Ann Arbor, Michigan 48109, USA.

Journal of biological chemistry (UNITED STATES) Sep 8 2000, 275 (36) p27823-31, ISSN 0021-9258 Journal Code: HIV

Contract/Grant No.: CA-64556, CA, NCI Languages: ENGLISH Document type: JOURNAL ARTICLE

Nod1 is an Apaf-1-like molecule composed of a caspase-recruitment domain (CARD), nucleotide-binding domain, and leucine-rich repeats that associates with the CARD -containing kinase RICK and activates nuclear factor kappaB (NF-kappaB). We show that self-association of Nod1 mediates proximity of RICK and the interaction of RICK with the gamma subunit of the IkappaB kinase (IKKgamma). Similarly, the RICK-related kinase RIP associated via its intermediate region with IKKgamma. A mutant form of IKKgamma deficient in binding to IKKalpha and IKKbeta inhibited NF-kappaB activation induced by RICK or RIP. Enforced oligomerization of RICK or RIP as well as of IKKgamma, IKKalpha, or IKKbeta was sufficient for induction of NF-kappaB activation. Thus, the proximity of RICK, RIP, and IKK complexes may play an important role for N -kappaB activation during Nod1 oligomerization or trimerization of the tumor necrosis factor alpha receptor.

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10133131 99292766

CLAP, a novel caspase recruitment domain-containing protein in the tumor necrosis factor receptor pathway, regulates NF-kappaB activation and apoptosis.

Srinivasula SM; Ahmad M; Lin JH; Poyet JL; Fernandes-Alnemri T; Tsichlis PN; Alnemri ES

Center for Apoptosis Research and the Department of Microbiology and Immunology, Kimmel Cancer Institute, Thomas Jefferson University, Philadelphia, Pennsylvania 19107, USA.

Journal of biological chemistry (UNITED STATES) Jun 18 1999, 274 (25) p17946-54, ISSN 0021-9258 Journal Code: HIV Contract/Grant No.: AG13487, AG, NIA

Languages: ENGLISH Document type: JOURNAL ARTICLE

Molecules that regulate NF-kappaB activation play critical roles in apoptosis and inflammation. We describe the cloning of the cellular homolog of the equine herpesvirus-2 protein E10 and show that both proteins regulate apoptosis and NF-kappaB activation. These proteins were found to contain N-terminal caspase-recruitment domains (CARDs) and novel C-terminal domains (CTDs) and were therefore named CLAPs (CARD -like apoptotic proteins). The cellular and viral CLAPs induce apoptosis downstream of caspase-8 by activating the Apaf-1-caspase-9 pathway and activate NF-kappaB by acting upstream of the NF-kappaB-inducing kinase, NIK, and the IkB kinase, IKKalpha. Deletion of either the CARD or the CTD domain inhibits both activities. The CARD domain was found to be important for homo- and heterodimerization of CLAPs. Substitution of the CARD domain with an inducible FKBP12 oligomerization domain produced a molecule that can induce NF-kappaB activation, suggesting that the CARD domain functions as an oligomerization domain, whereas the CTD domain functions as the effector domain in the NF-kappaB activation pathway. Expression of the CARD domain of human CLAP abrogates tumor necrosis factor-alpha-induced NF-kappaB activation, suggesting that cellular CLAP plays an essential role in this pathway of NF-kappaB activation.

9/7/4 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.

10080727 97318595

The CARD domain: a new apoptotic signalling motif.

Hofmann K; Bucher P; Tschopp J

Swiss Institute for Experimental Cancer Research, University of Lausanne, Switzerland.

Trends in biochemical sciences (ENGLAND) May 1997, 22 (5) p155-6, ISSN 0968-0004 Journal Code: WEF

Languages: ENGLISH Document type: JOURNAL ARTICLE

9/7/5 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.

09935057 99272740

Identification of RIP3, a RIP-like kinase that activates apoptosis and NFkappaB.

Yu PW; Huang BC; Shen M; Quast J; Chan E; Xu X; Nolan GP; Payan DG; Luo Y

Rigel, Inc. 240 East Grand Ave, South San Francisco, California 94080, USA.

Current biology (ENGLAND) May 20 1999, 9 (10) p539-42, ISSN 0960-9822 Journal Code: B44 Languages: ENGLISH Document type: JOURNAL ARTICLE

The tumor necrosis factor receptor 1 (TNFR1) and the Fas receptor recruit complexes formed by the interactions between RIP kinase, TRADD, FADD and RAIDD - adaptor proteins that contain death domains - which in turn recruit other proteins to initiate signaling [1][2][3][4][5]. To identify proteins associated with the TNF signaling pathway, we performed a yeast two-hybrid interaction screen using RIP as bait. We isolated a kinase, RIP3, which shares homology with the kinase domain of RIP and RIP2 (also known as Rick or CARDIAK). RIP3 could be co-immunoprecipitated with RIP, TRAF2 and TNFR1 in mammalian cells. The carboxy-terminal domain of RIP3, like that of RIP, could activate the transcription factor NFkappaB and induce apoptosis when expressed in mammalian cells. Interestingly, this region shares no significant sequence homology to the death domain of RIP, the caspase-recruiting domain (CARD) of RIP2 [6][7][8] or any other apoptosis-inducing domain. As with RIP and RIP2, the kinase domain of RIP3 was not required for either NFkappaB activation or apoptosis induction. Overexpression of a dominant-negative mutant of RIP3 strongly inhibited the caspase activation but not the NFkappaB activation induced by TNFalpha. Therefore, RIP3 appears to function as an intermediary in TNFalpha-induced apoptosis.

9/7/6 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.

09815630 99142601

Bcl10 is involved in t(1;14)(p22;q32) of MALT B cell lymphoma and mutated in multiple tumor types [see comments]

Willis TG; Jadayel DM; Du MQ; Peng H; Perry AR; Abdul-Rauf M; Price H; Karran L; Majekodunmi O; Wlodarska I; Pan L; Crook T; Hamoudi R; Isaacson PG; Dyer MJ

Academic Department of Haematology and Cytogenetics, Institute of Cancer Research, Sutton, Surrey, United Kingdom.

Cell (UNITED STATES) Jan 8 1999, 96 (1) p35-45, ISSN 0092-8674 Journal Code: CQ4 Comment in Cell 1999 Jun 11;97(6):683-4; discussion 686-8; Comment in: Cell 1999 Jun 11;97(6):684-6; discussion 686-8 Languages: ENGLISH Document type: JOURNAL ARTICLE

MALT B cell lymphomas with t(1;14)(p22;q32) showed a recurrent breakpoint upstream of the promoter of a novel gene, Bcl10. Bcl10 is a cellular homolog of the equine herpesvirus-2 E10 gene: both contain an amino-terminal caspase recruitment domain (CARD) homologous to that found in several apoptotic molecules. Bcl10 and E10 activated NF-kappaB but caused apoptosis of 293 cells. Bcl10 expressed in a MALT lymphoma exhibited a frameshift mutation resulting in truncation distal to the CARD . Truncated Bcl10 activated NF-kappaB but did not induce apoptosis. Wild-type Bcl10 suppressed transformation, whereas mutant forms had lost this activity and displayed gain-of-function transforming activity. Similar mutations were detected in other

tumor types, indicating that Bcl10 may be c[illegible]ly involved in the pathogenesis of human malignancy.

9/7/7 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
09677800 98435292
Apoptosis and expression of bcl-2 protein are inverse factors influencing tumour cell turnover in primary carcinoid tumours of the lung.
Zirbes TK; Lorenzen J; Baldus SE; Moenig SP; Wolters U; Ottlik A; Thiele J; Holscher AH; Dienes HP
Department of Pathology, University of Cologne, Germany.
Histopathology (ENGLAND) Aug 1998, 33 (2) p123-8, ISSN 0309-0167
Journal Code: GB4 Languages: ENGLISH Document type: JOURNAL ARTICLE
AIMS: This study evaluates potential regulating factors in primary pulmonary carcinoid tumours, 16 typical and four atypical samples, with special emphasis on apoptosis and the bcl-2 gene family. Furthermore, p53-related oncogenes were analysed in a search for associated biological parameters. METHODS AND RESULTS: The in-situ end-labelling technique (ISEL) was used to determine apoptotic cells, in addition to immunohistochemical methods, which were used to investigate the expression of the Ki67 antigen (avidinbiotin complex (ABC) method) and bcl-2, bcl-x, p53, p21/waf1, p27 and mdm-2 proteins (catalysed reporter deposition (CARD) technique). The incidence of apoptotic tumour cells was significantly enhanced in typical carcinoids. The bcl-2 protein was expressed to a higher degree in atypical carcinoids, which displayed a higher proliferative capacity as well. In contrast, bcl-x was observed predominantly in so-called typical carcinoids. The tumour cell turnover index was the most distinguishing parameter between both entities. All carcinoid tumours failed to show a staining for p53, p21/waf. p27 and mdm-2 proteins. CONCLUSIONS: The different biological behaviour of the carcinoid tumours under study seems to be influenced by the bcl-2 gene family preventing programmed cell death. We speculate that this results in a more aggressive course in atypical carcinoid tumours.

9/7/8 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
09562441 98307936
RIP2 is a novel NF-kappaB-activating and cell death-inducing kinase.
McCarthy JV; Ni J; Dixit VM
Department of Pathology, University of Michigan Medical School, Ann Arbor, Michigan 48109-0602, USA.
Journal of biological chemistry (UNITED STATES) Jul 3 1998, 273 (27) p16968-75, ISSN 0021-9258 Journal Code: HIV Languages: ENGLISH
Document type: JOURNAL ARTICLE
Through specific interactions with members of the tumor necrosis receptor (TNFR) family, adapter molecules such as the serine/threonine (Ser/Thr) kinase RIP mediate divergent signaling pathways including NF-kappaB activation and cell death. In this study, we have identified and characterized a novel 61-kDa protein kinase related to RIP that is a component of both the TNFR-1 and the CD40 signaling complexes. Receptor interacting protein-2 (RIP2) contains an N-terminal domain with homology to Ser/Thr kinases and a C-terminal caspase activation and recruitment domain (CARD), a homophilic interaction motif that mediates the recruitment of caspase death proteases. Overexpression of RIP2 signaled both NF-kappaB activation and cell death. Mutational analysis revealed the pro-apoptotic function of RIP2 to be restricted to its C-terminal CARD domain, whereas the intact molecule was necessary for NF-kappaB activation. RIP2 interacted with other members of the TNFR-1 signaling complex, including inhibitor of apoptosis protein cIAP1 and with members of the TNFR-associated factor (TRAF) family, specifically TRAF1, TRAF5, and TRAF6, but not with TRAF2, TRAF3, or TRAF4. These TRAF interactions mediate the recruitment of RIP2 to receptor signaling complexes.

9/7/9 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
09541168 98307385
Mutational analysis of Caenorhabditis elegans CED-4.
Seshagiri S; Chang WT; Miller LK
Department of Entomology, The University of Georgia, Athens 30602, USA.
FEBS letters (NETHERLANDS) May 22 1998, 428 (1-2) p71-4, ISSN 0014-5793 Journal Code: EUH Languages: ENGLISH
Document type: JOURNAL ARTICLE
Much of our knowledge concerning the genetics that regulate cell death has come from the studies of cell death during the development of the nematode Caenorhabditis elegans. Of the 14 genes identified as components of nematode cell death pathways, two genes, ced-3 and ced-4, are required to promote cell death and a third, ced-9, blocks cell death. Recent studies show CED-4 to be an activator of CED-3 and CED-9 to be an inhibitor of CED-4. Two published sequence alignments suggest that CED-4 contains a death effector domain (DED), a protein sequence motif present in other death signaling proteins like Fadd and Flice; one study suggests a DED sequence similarity near the N-terminus while the other found sequence similarity near the C-terminus of CED-4. Using mutational analysis we have tested the functional significance of the conserved residu[illegible]nd within the putative DEDs of CED-4. Mutations in two conserved residues within the putative N-terminal DED of CED-4 affected its function, while mutations in the conserved residues within the putative C-terminal DED had no effect on CED-4 function. Our results do not support the presence of a DED in the C-terminus of CED-4 and suggest a potential role for the N-terminus in CED-4 function, possibly as a DED or as a CARD (caspase recruitment domain). We also found that CED-9 associated with all the CED-4 mutants and inhibited the activity of all the active-CED-4 mutants.

10/7/1 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
10837585 21153744
A Novel Enhancer of the Apafl Apoptosome Involved in Cytochrome c-dependent Caspase Activation and Apoptosis.
Chu ZL; Pio F; Xie Z; Welsh K; Krajewska M; Krajewski S; Godzik A; Reed JC
Burnham Institute, La Jolla, California 92037.
Journal of biological chemistry (United States) Mar 23 2001, 276 (12) p9239-45, ISSN 0021-9258 Journal Code: HIV Languages: ENGLISH
Document type: Journal Article
Apafl/CED4 family members play central roles in apoptosis regulation as activators of caspase family cell death proteases. These proteins contain a nucleotide-binding (NB) self-oligomerization domain and a caspase recruitment domain (CARD). A novel human protein was identified, NAC, that contains an NB domain and CARD . The CARD of NAC interacts selectively with the CARD domain of Apafl, a caspase-activating protein that couples mitochondria-released cytochrome c (cyt-c) to activation of cytosolic caspases . Cyt-c-mediated activation of caspases in cytosolic extracts and in cells is enhanced by overexpressing NAC and inhibited by reducing NAC using antisense/DNAzymes. Furthermore, association of NAC with Apafl is cyt c-inducible, resulting in a mega-complex (>1 MDa) containing both NAC and Apafl and correlating with enhanced recruitment and proteolytic processing of pro-caspase-9. NAC also collaborates with Apafl in inducing caspase activation and apoptosis in intact cells, whereas fragments of NAC representing only the CARD or NB domain suppress Apafl-dependent apoptosis induction. NAC expression in vivo is associated with terminal differentiation of short lived cells in epithelia and some other tissues. The ability of NAC to enhance Apafl-apoptosome function reveals a novel paradigm for apoptosis regulation.

10/7/2 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
10292695 20047184
Solution structure and mutagenesis of the caspase recruitment domain (CARD) from Apaf-1.
Day CL; Dupont C; Lackmann M; Vaux DL; Hinds MG
Institute of Molecular BioSciences, Massey University, Private Bag 11 222, Palmerston North, New Zealand.
Cell death and differentiation (ENGLAND) Nov 1999, 6 (11) p1125-32 ISSN 1350-9047 Journal Code: C7U Languages: ENGLISH
Document type: JOURNAL ARTICLE
Activation of procaspase-9, a key component of the apoptosis mechanism, requires the interaction of its caspase recruitment domain (CARD) with the CARD in the adaptor protein Apaf-1. Using nuclear magnetic resonance spectroscopy and mutagenesis we have determined the structure of the CARD from Apaf-1 and the residues important for binding the CARD in procaspase-9. Apaf-1's CARD contains seven short alpha-helices with the core six helices arranged in an antiparallel manner. Residues in helix 2 have a central role in mediating interaction with procaspase-9 CARD . This interaction surface is distinct from that proposed based on the structure of the CARD from RAIDD, but is coincident with that of the structurally similar FADD death effector domain and the Apaf-1 CARD interface identified by crystallographic studies.

10/7/3 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
10109924 98359117
Solution structure of the RAIDD CARD and model for CARD/ CARD interaction in caspase-2 and caspase-9 recruitment.
Chou JJ; Matsuo H; Duan H; Wagner G
Committee on Higher Degrees in Biophysics, Harvard University, Cambridge, Massachusetts 02138, USA.
Cell (UNITED STATES) Jul 24 1998, 94 (2) p171-80, ISSN 0092-8674
Journal Code: CQ4 Contract/Grant No.: GM 38608, GM, NIGMS; GM 47467, GM, NIGMS Languages: ENGLISH Document type: JOURNAL ARTICLE
Apoptosis requires recruitment of caspases by receptor-associated adaptors through homophilic interactions between the CARDs (caspase recruitment domains) of adaptor proteins and prodomains of caspases . We have solved the CARD structure of the RAIDD adaptor protein that recruits ICH-1/caspase-2. It consists of six tightly packed helices arranged in a topology homologous to the Fas death domain. The surface contains a basic and an acidic patch on opposite sides. This polarity is conserved in the ICH-1 CARD as indicated by homology modeling. Mutagenesis data suggest that these patches mediate CARD /CARD

interaction between RAIDD and ICH-1. Subs[illegible]modeling of the CARDs of Apaf-1 and caspase-9, as well as Ced-4 and Ced-3, showed that the basic/acidic surface polarity is highly conserved, suggesting a general mode for CARD CARD interaction.

10/7/4 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
10069427 99432221
Solution structure of Apaf-1 CARD and its interaction with caspase-9 CARD: a structural basis for specific adaptor/caspase interaction.
Zhou P; Chou J; Olea RS; Yuan J; Wagner G
Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA 02115, USA.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Sep 28 1999, 96 (20) p11265-70, ISSN 0027-8424
Journal Code: PV3 Contract/Grant No.: GM 38608, GM, NIGMS Languages: ENGLISH Document type: JOURNAL ARTICLE
Direct recruitment and activation of caspase-9 by Apaf-1 through the homophilic CARD / CARD (Caspase Recruitment Domain) interaction is critical for the activation of caspases downstream of mitochondrial damage in apoptosis. Here we report the solution structure of the Apaf-1 CARD domain and its surface of interaction with caspase-9 CARD . Apaf-1 CARD consists of six tightly packed amphipathic alpha-helices and is topologically similar to the RAIDD CARD , with the exception of a kink observed in the middle of the N-terminal helix. By using chemical shift perturbation data, the homophilic interaction was mapped to the acidic surface of Apaf-1 CARD centered around helices 2 and 3. Interestingly, a significant portion of the chemically perturbed residues are hydrophobic, indicating that in addition to the electrostatic interactions predicted previously, hydrophobic interaction is also an important driving force underlying the CARD /CARD interaction. On the basis of the identified functional residues of Apaf-1 CARD and the surface charge complementarity, we propose a model of CARD /CARD interaction between Apaf-1 and caspase-9.

10/7/5 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
09894479 99251581
Inactivating mutations and overexpression of BCL10, a caspase recruitment domain-containing gene, in MALT lymphoma with t(1;14)(p22;q32).
Zhang Q; Siebert R; Yan M; Hinzmann B; Cui X; Xue L; Rakestraw KM; Naeve CW; Beckmann G; Weisenburger DD; Sanger WG; Nowotny H; Vesely M; Callet-Bauchu E; Salles G; Dixit VM; Rosenthal A; Schlegelberger B; Morris SW
Department of Pathology and Laboratory Medicine, St. Jude Children's Research Hospital, Memphis, Tennessee 38105, USA.
Nature genetics (UNITED STATES) May 1999, 22 (1) p63-8, ISSN 1061-4036 Journal Code: BRO Contract/Grant No.: CA-27165, CA, NCI
Languages: ENGLISH Document type: JOURNAL ARTICLE
Mucosa-associated lymphoid tissue (MALT) lymphomas most frequently involve the gastrointestinal tract and are the most common subset of extranodal non-Hodgkin lymphoma (NHL). Here we describe overexpression of BCL10, a novel apoptotic signalling gene that encodes an amino-terminal caspase recruitment domain (CARD), in MALT lymphomas due to the recurrent t(1;14)(p22;q32). BCL10 cDNAs from t(1;14)-positive MALT tumours contained a variety of mutations, most resulting in truncations either in or carboxy terminal to the CARD . Wild-type BCL10 activated NF-kappaB but induced apoptosis of MCF7 and 293 cells. CARD -truncation mutants were unable to induce cell death or activate NF-kappaB, whereas mutants with C-terminal truncations retained NF-kappaB activation but did not induce apoptosis. Mutant BCL10 overexpression might have a twofold lymphomagenic effect: loss of BCL10 pro-apoptosis may confer a survival advantage to MALT B-cells, and constitutive NF-kappaB activation may provide both anti-apoptotic and proliferative signals mediated via its transcriptional targets.

12/7/1 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
10909476 21153743
Molecular cloning and characterization of defcap-l and -s, two isoforms of a novel member of the mammalian ced-4 family of apoptosis proteins.
Hlaing T; Guo RF; Dilley KA; Loussia JM; Morrish TA; Shi MM; Vincenz C; Ward PA
Department of Pathology, University of Michigan Medical School, the Department of Human Genetics, University of Michigan Medical School, Ann Arbor, Michigan 48109, USA.
Journal of biological chemistry (United States) Mar 23 2001, 276 (12) p9230-8, ISSN 0021-9258 Journal Code: HIV Languages: ENGLISH
Document type: Journal Article
We report the deduced amino acid sequences of two alternately spliced mammalian apoptosis -promoting machinery.

12/7/2 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
10882398 21164730
Apaf-1XL Is an Inactive Isoform Compared with Apaf-1L.
Fu WN; Kelsey SM; Newland AC; Jia L
Department of Haematology/Oncology, St. Bartholomew's and Royal London School of Medicine and Dentistry, Turner Street, London, E1 2AD, United Kingdom
Biochemical and biophysical research communications (United States) Mar 23 2001, 282 (1) p268-72, ISSN 0006-291X Journal Code: 9Y8 Languages: ENGLISH Document type: Journal Article
Apaf-1 plays a crucial role in the cytochrome c/dATP-dependent activation of caspase-9 and -3. We found that the human myeloid leukemic K562 cells were more resistant to cytochrome c-induced activation of caspase-9 and -3 in a cell-free system compared with the human T-lymphoblastic subclone CEM/VLB(100) cells. Apaf-1 cDNA sequencing revealed an additional insert of 11 aa between the CARD and CED-4 (ATPase) domains in K562 cells, which was identical to the sequence of Apaf-1XL. Immunoprecipitation of Apaf-1 with caspase-9 after a cell-free reaction demonstrated that Apaf-1XL in the K562 cell line showed a lower binding ability to caspase-9 compared with Apaf-1L protein. The resistance of K562 cells to cytochrome c-dependent apoptosis may be partly due to this Apaf-1XL form. These results suggest that the additional insert between CARD and CED-4 domains might affect Apaf-1 recruitment of caspase-9 during apoptosis . Copyright 2001 Academic Press.

12/7/3 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
10828281 21097719
Bcl10 is a positive regulator of antigen receptor-induced activation of NF-kappaB and neural tube closure.
Ruland J; Duncan GS; Elia A; del Barco Barrantes I; Nguyen L; Plyte S; Millar DG; Bouchard D; Wakeham A; Ohashi PS; Mak TW
Amgen Institute, 620 University Avenue, Toronto, Ontario, Canada M5G 2C1.
Cell (United States) Jan 12 2001, 104 (1) p33-42, ISSN 0092-8674 Journal Code: CQ4 Languages: ENGLISH Document type: Journal Article
Bcl10, a CARD -containing protein identified from the t(1;14)(p22;q32) breakpoint in MALT lymphomas, has been shown to induce apoptosis and activate NF-kappaB in vitro. We show that one-third of bcl10-/- embryos developed exencephaly, leading to embryonic lethality. Surprisingly, bcl10-/- cells retained susceptibility to various apoptotic stimuli in vivo and in vitro. However, surviving bcl10-/- mice were severely immunodeficient and bcl10-/- lymphocytes are defective in antigen receptor or PMA/Ionomycin-induced activation. Early tyrosine phosphorylation, MAPK and AP-1 activation, and Ca2+ signaling were normal in mutant lymphocytes, but antigen receptor-induced NF-kappaB activation was absent. Thus, Bcl10 functions as a positive regulator of lymphocyte proliferation that specifically connects antigen receptor signaling in B and T cells to NF-kappaB activation.

12/7/4 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
10787146 21108750
The DAPIN family: a novel domain links apoptotic and interferon response proteins.
Staub E; Dahl E; Rosenthal A
metaGen Gesellschaft fur Genomforschung mbH, 14195, Berlin, Germany
Trends in biochemical sciences (England) Feb 2001, 26 (2) p83-5, ISSN 0968-0004 Journal Code: WEF Languages: ENGLISH
Document type: Journal Article
We report the discovery of a protein domain, hereafter referred to as DAPIN, in diverse vertebrate and viral proteins that is associated with tumor biology, apoptosis and inflammation. Based on a secondary structure prediction, we suggest an all-alpha fold for DAPIN, which is also adopted by apoptotic protein domains of the CARD , death domain and death effector domain type.

12/7/5 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
10702167 20580347
Murine ortholog of ASC, a CARD-containing protein, self-associates and exhibits restricted distribution in developing mouse embryos.
Masumoto J; Taniguchi S; Nakayama K; Ayukawa K; Sagara J
Department of Molecular Oncology and Angiology, Second Department of Anatomy, Research Center on Aging and Adaptation, Shinshu University School of Medicine, Asahi 3-1-1, Matsumoto, Nagano, 390-8621, Japan.
Experimental cell research (UNITED STATES) Jan 15 2001, 262 (2) p128-33, ISSN 0014-4827 Journal Code: EPB
Languages: ENGLISH Document type: Journal Article
ASC (apoptosis -associated speck-like protein containing a CARD) was first identified as a cytosolic soluble protein that forms insoluble aggregates and enhances etoposide-induced apoptosis . We have cloned a murine ortholog of ASC (mASC) comprising 193 amino acids with a well-conserved pyrin N-terminal homology domain and caspase recruitment domain (CARD). mASC fused with green fluorescent protein appeared as a speck in transfected COS-7 cells and showed self-association. We analyzed mASC gene expression in developing embryos by in situ hybridization and found it to have a restricted

distribution in mouse embryos. At E9.5, m[redacted]s strongly expressed in the telencephalon, thalamic areas of the diencephalon, heart, and liver. Northern blotting analysis revealed that the mASC gene was expressed ubiquitously in multiple organs in adult mice. These findings indicate that mASC shows conservation of not only the primary structure of human ASC but also the ability to aggregate and has some similarity in its distribution to other CARD -containing molecules, including the apoptosis regulator Apaf-1. Copyright 2001 Academic Press.

12/7/6 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
09992307 99329013
c-E10 is a caspase-recruiting domain-containing protein that interacts with components of death receptors signaling pathway and activates nuclear factor-kappaB.
Costanzo A; Guiet C; Vito P
Fondazione A. Cesalpino, I Clinica Medica, V.le Policlinico 155, 00161 Roma, Italy.
Journal of biological chemistry (UNITED STATES) Jul 16 1999, 274 (29) p20127-32, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH Document type: JOURNAL ARTICLE
Members of the tumor necrosis factor receptor superfamily induce apoptosis via interaction with FADD and regulate cell growth and differentiation through TRADD and TRAFs molecules. While screening for molecules involved in the regulation of death receptor signaling, we identified a novel protein, c-E10. c-E10 contains an amino-terminal caspase-recruiting domain (CARD) and shares a sequence homologous with E10, a viral CARD -containing protein that binds to c-E10. In transfection experiments c-E10 oligomerizes, binds to the cytoplasmic portion of TRAIL receptor 1 (DR4) and coprecipitates with TRADD. Expression of c-E10 under the control of a doxycycline-dependent transcriptional transactivator results in NF-kappaB activation, which is inhibited by dominant negative forms of TRAF2 and NIK kinase. Thus, our results suggest that c-E10 is an adapter protein that activates NF-kappaB through a molecular pathway involved in death receptor signaling.

12/7/7 DIALOG(R)File 155:MEDLINE(R) (c) format only 2000 Dialog Corporation. All rts. reserv.
09648932 97294237
Systemic lupus erythematosus: immunopathogenesis and the card game analogy.
Isenberg DA
Department of Medicine, University College London, UK.
Journal of rheumatology. Supplement (CANADA) May 1997, 48 p62-6, ISSN 0380-0903 Journal Code: JWY Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Systemic lupus erythematosis (SLE) is a multifactorial disease with both genetic and environmental etiology. The complexity of factors contributing to SLE are considered in an analogy with a card game. The hears suit represents sex hormones. SLE is a disease of marked female prevalence and abnormal estrogen metabolism has been described in women with SLE. The clubs suit considers complement and other genetic factors. Increased risk of SLE has been described in association with some HLA markers and the complement C4A0 null allele. Although convincing evidence has not yet emerged, other candidate genes of importance are T cell receptor genes and genes encoding B cell immunoglobulin receptors and antibodies. Recently, abnormalities of apoptosis and of expression of the protooncogene Bcl-2 have been investigated. Overall different genes have been shown to increase the risk of SLE, and/or to influence the development of particular antibodies, and particular subsets of disease. The diamonds suit considers antigens and antibodies in the etiopathogenesis of SLE. Numerous autoantibodies have been described that bind a variety of targets on the cell surface, within the cytoplasm, or in the nucleus. It is generally agreed that autoantibodies develop as a consequence of both generalized polyclonal activation and antigen drive. The final suit of spades considers infectious, environmental, and other agents such as drugs, as triggers in the development of SLE. (27 Refs.)

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